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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,782	07/09/2001	Susan Hardin	IVGN1013	9388

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TROUTMAN SANDERS LLP
600 Peachtree Street
Suite 5200
Atlanta, GA 30308

EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
06/08/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jim.schutz@troutmansanders.com
ryan.schneider@troutmansanders.com
patents@troutmansanders.com

Office Action Summary	Application No.	Applicant(s)	
	09/901,782	HARDIN ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *See Continuation Sheet* is/are rejected.

8)☒ Claim(s) *66* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☒ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *10 September 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 10,16-18,50,51,53-55,64,65,67-69,71,72,74,76,77,79-82,84-87,89-92,95-98,100,102-106 and 108-111.

Continuation of Disposition of Claims: Claims rejected are 10,16-18,50,51,53-55,64,65,67-69,71,72,74,76,77,79-82,84-87,89-92,95-98,100,102-106 and 108-111.

DETAILED ACTION

Specification

1. Applicant is reminded of the proper content of an abstract of the disclosure.

2. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

3. The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

4. Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

5. Extensive mechanical and design details of apparatus should not be given.

Response to argument

6. Applicant, at page 10 of the response of 02 March 2012, hereinafter the response, asserts:

> The *Abstract* should be directed to the **technical disclosure** of the Application. Neither 37 C.F.R. nor the MPEP require that the *Abstract* align itself with the claimed subject matter. 37 C.F.R. § 1.72 states clearly that the "purpose of the abstract is to enable the United States Patent and Trademark Office and the public generally to determine quickly from a cursory inspection the nature and gist of the technical disclosure."

7. For convenience, the abstract is reproduced below.

> A sequencing methodology is disclosed that allows a single DNA or RNA molecule or portion thereof to be sequenced directly and in substantially real time. The methodology involves engineering a polymerase and/or dNTPs with atomic and/or molecular tags that have a detectable property that is monitored by a detection system.

8. Agreement is reached in that the abstract is not required to be aligned with the claims. However, the abstract does need to be reflective of the entirety of the technical disclosure of the subject application.

9. In the present case, the abstract only refers to sequencing methodology, which in and of itself is understandable as the disclosure is, at least in part, directed to same. However, not one of the 45 claims pending in the subject application is directed to any method, be it for sequencing or otherwise. Accordingly, at least some part of the technical disclosure (see, e.g., pages 23-26 of the specification as filed, and original claims 1-24) is also directed to compositions, which are claimed and which are not reflected in the abstract.

Claim Objections

10. Claim 66 is objected to because of the following informalities: The current claim listing does not account for claim 66. Appropriate correction is required.

Drawings

11. The drawings were received on 10 September 2010. These drawings are acceptable.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 17, 54, 68, 76, 79, 80, 85, 86, 87, 90, 91, 96, 97, 105, 106 and 108-111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claims 17, 54, 68, 76, and 97 are indefinite as a result of the use of the term “comprises.” As presently worded, one of skill in the art would not be able to readily determine the metes and bounds of the "fluorescent property." Similarly, claims 85-87 are indefinite as a result to the use of the term "comprises" as it is not readily apparent what constitutes the metes and bounds of the recited groups.

15. The term "about" in claim s 79, 80, 81, 89, 90, 91, 105, and 106 is a relative term which renders the claims indefinite. The term "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Attention is directed to MPEP 2173.05(b)A, which states in part:

> In determining the range encompassed by the term "about", one must consider the context of the term as it is used in the specification and claims of the application. *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1326, 81 USPQ2d 1427, 1432 (Fed. Cir. 2007). In< *W. L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), the court held that a limitation defining the stretch rate of a plastic as “exceeding about 10% per second” is definite because infringement could clearly be assessed through the use of a stopwatch. However, the court held that claims reciting “at least about” were invalid for indefiniteness where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term “about.”

Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991).

16. "The use of the word 'about,' avoids a strict numerical boundary to the specified parameter." *Ortho-McNeil Pharmaceutical, Inc. v. Caraco Pharmaceutical Laboratories, Ltd.,* 476 F.3d 1321, 1326 (Fed. Cir. 2007) (quoting *Pall Corp. v. Micron Separations, Inc.,* 66 F.3d 1211, 1217 (Fed. Cir. 1995)); *see also In re Harris,* 409 F.3d 1339, 1343 (Fed. Cir. 2005) ("[U]se of the term 'about' shows that the applicants did not intend to limit the claimed ranges to their exact end-points.").

17. However, "the word 'about' does not have a universal meaning in patent claims[;]" rather, "the meaning depends on the technological facts of the particular case." *Pall Corp.,* 66 F.3d at 1217; *see also Eiselstein v. Frank,* 52 F.3d 1035, 1040 (Fed. Cir. 1995) ("The meaning of the word 'about' is dependent on the facts of a case, the nature of the invention, and the knowledge imparted by the totality of the.., disclosure to those skilled in the art."). Thus, in evaluating the scope of the "about," it is appropriate to look how the Specification and other claims use the term, as well as considering the effects of varying the parameter described by the term. *Pall Corp.,* 66 F.3d at 1217.

18. Claims 10, 50, 64, 71, 79, and 89 are indefinite with respect to what constitutes the meets and bounds of “change” as it relates to a "change" in a “fluorescent property.” Acknowledgement is made of dependent claims 17, 54, 68, 76, and 97 providing a non-limiting group of alternative properties. However, the remaining dependent claims are not so limited. Accordingly, it is not readily apparent as to just what “fluorescent properties” are being

encompassed by not only the independent claims and those of the dependent claims, keeping in mind the requirements of 35 USC 112, fourth paragraph.

19. Claims 108-111 are indefinite with respect to what constitutes the metes and bounds of "a native polymerase." Said claims are also indefinite with respect to how the polymerase is to be construed as "native" when it has undergone mutation.

20. Claims 108-111 are indefinite with respect to what constitutes the metes and bounds of "involved."

21. Claims 108-111 are indefinite with respect to what constitutes the metes and bounds of "cysteine residue replacement" and "cysteine residue replacements."

Response to argument

22. At page 11 of the repose of 02 March 2012, hereinafter the response, applicant's representative asserts:

> Moreover, unless the patentee is acting is its own lexicographer, the claims should be given their ordinary and customary meaning as understood by one of ordinary skill in the art at the time of the invention. MPEP§2111.01 (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc.))

23. This argument has been fully considered and has not been found persuasive. As set forth above, there is no one set definition to be ascribed to the term "about." Further, applicant has not presented any showing that there is but one definition, much less state on the record just what that "ordinary and customary" definition is.

24. At page 12 of the response applicant's representative asserts:

> Relative terminology is acceptable when one of ordinary skill would understand what is claimed. In this instance, one of ordinary skill will understand what "about X angstroms" would mean.

25. It is noted that applicant has not directed attention to where applicant has provided any definition of the term, nor has directed attention to any one definition found in the art that "one of ordinary skill would understand." Attention is directed to MPEP 2145.

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
> The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained.

26. At page 11, bridging to page 12, of the response, argument is presented as to the combination of "fluorescent property" and "comprises" are definite as "a duration, intensity and/or frequency of emitted light" clearly define the claim.

27. The above argument has been considered and has not been found persuasive. The issue is not that "a duration, intensity, and/or frequency' are indefinite, rather, the issue of definiteness centers on the use of the term "comprising" which allows for the inclusion of other, unrecited elements/factors. It is the nature of the claim encompassing factors that are not described and are undefined that proscribes the public from being readily able to determine the metes and bounds of the claims.

28. For the above reasons and in the absence of convincing evidence to the contrary, the rejection is maintained.

29. At page 12 of the response, applicant's representative asserts that one of skill in the art would understand the metes and bounds to be ascribed to the term "change" in a "fluorescent property."

30. The above argument has not been found persuasive. Attention is directed to MPEP 2145.

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
> The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

31. At page 12 of the response, applicant's representative asserts:

> Applicants submit that one of ordinary skill in the art would recognize that a "native polymerase" is a polymerase isolated from a native source, as opposed to a recombinant or modified polymerase.

The above argument has been considered and has not been found persuasive as it relates to the claims at issue (claims 108-111). It is noted with particularity that independent claim 108 states in part: "[T]he polymerase comprises a genetically engineered polymerase comprising a native polymerase." By applicant's own definition, the two cannot be the same, yet by the claims requirement, that which is genetically engineered comprises the "native polymerase." Given this conflict, the claim is deemed indefinite.

32. Acknowledgement is also made of applicant's representative making further, unsubstantiated assertions as to what one of skill in the art would have understood and interpreted terms to mean. Attention is again directed to MPEP 2145, *supra*.

33. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

34. Claims 10, 16-18, 50, 51, 53-55, 64-69, 71, 72, 74, 76, 77, 102, 103 and 108-111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

35. As a result of the amendment of 02 March 2012, dependent claims 108-111 have been amended. Said dependent claims 108-111 depend from independent claims 10, 50, 64, and 71, respectively. In recognition that an independent claim must encompass all embodiments of each and every claim that depends therefrom, the amendment to said dependent claims has been construed as an amendment upon the scope of the independent claims from which they each depend.

36. As set forth in *In re Alonso* 88 USPQ2d 1849 (Fed. Cir. 2008), at 1851:

> The written description requirement of 35 U.S.C. § 112, ¶ 1, is straightforward: "The specification shall contain a written description of the invention …." To satisfy this requirement, the specification must describe the invention in sufficient detail so "that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997); *see also LizardTech, Inc. v. Earth Res. Mapping, Inc.*,

> 424 F.3d 1336, 1345 [76 USPQ2d 1724] (Fed. Cir. 2005); *Eiselstein v. Frank*, 52 F.3d 1035, 1039 [34 USPQ2d 1467] (Fed. Cir. 1995).

Alonso at 1852:

> A genus can be described by disclosing: (1) a representative number of species in that genus; or (2) its "relevant identifying characteristics," such as "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Enzo*, 323 F.3d at 964.

37. In applying the test as set forth in *Alonso*, it is noted that dependent claims 108-111 now require the "genetically engineered polymerase compris[es] a native polymerase with one cysteine residue replacement or a plurality of cysteine residue replacements at one site or a plurality of sites of the native polymerase, where the site or sites are not in contact with other proteins, where the site or sites do not alter the conformation or folding of the polymerase, where the site or sites are not involved in the functioning of the polymerase, and wherein the polymerase tag is bonded to the polymerase through a cysteine residue replacement or through a plurality of cysteine residue replacements."

38. The "native polymerase" can be form virtually and every conceivable source, which includes any plant, animal, bacterium and/or virus, be it a DNA polymerase or a reverse transcriptase. "Viruses" (Wikipedia.com, accessed 18 April 2012), teaches:

> An enormous variety of genomic structures can be seen among viral species; as a group, they contain more structural genomic diversity than plants, animals, archaea, or bacteria. <u>There are millions of different types of viruses, although only about 5,000 of them have been described in detail</u>. (Emphasis added)

"How many species of bacteria are there" (wisegeek.com; accessed 23 September 2011) teaches:

> Currently, estimates of the total number of species of bacteria range from about 10 million to a billion, but these estimates are tentative, and may be off by many orders of magnitude. By comparison, there are probably between 10 and 30 million species of animals, the vast majority of them insects. The number of scientifically recognized

species of animals is about 1,250,000. There are almost 300,000 recognized species of plants.

39. Review of the disclosure finds a Sequence Listing comprised of some 57 sequences. Of the 57 sequences provided, only SEQ ID NO. 11 appears to be full-length amino acid sequence for a protein encoded by *Thermus aquaticus*. A review of the specification fails to find where applicant has identified all applicable sites that a cysteine replacement can be performed, be it "at one site or a plurality of sites of the native polymerase" for this one polymerase, much less provide the amino acid, for any other polymerase, be it of viral, bacterial, plant, and/or animal (eukaryotic) origin.

40. It is further noted that the specification does not teach the encoding nucleotide sequence for any polymerase, much less identify those encoding position(s) where "at one site of a plurality of sites of the native polymerase," and lesser still, the application has not been found to disclose means and methods whereby functional "genetically engineered polymerases" are actually produced and have the requisite activity and "where the site or sites are not in contact with other proteins, where the site or sites do not alter the conformation or folding of the polymerase, where the site or sites are not involved in the functioning of the polymerase, and where the polymerase tag is bonded to the polymerase through a cysteine residue replacement or through a plurality of cysteine residue replacements."

41. Applicant's failure to disclose any example of any modified reverse transcriptase, or any viral, animal, or plant polymerase that has any of the applicable replacements, has not been found to satisfy either prong of the test as set forth in *Alonso*.

Claim Rejections - 35 USC § 102

42. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

43. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

44. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

45. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

46. Claims 10, 17 and 18 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 7,033,764 B2 (Korlach et al.).

47. The instant application claims benefit of priority to provisional application 60/216,594, foiled 07 July 2000. Korlach et al., claims benefit of priority to Provisional Application 60/134,827, filed 19 May 1999. Accordingly, Korlach et al., qualifies as 102(e)-type art.

48. Korlach et al., abstract, teaches:

> The present invention is directed to a method of sequencing a target nucleic acid molecule having a plurality of bases. In its principle, the temporal order of base additions during the polymerization reaction is measured on a molecule of nucleic acid, i.e. the activity of a nucleic acid polymerizing enzyme on the template nucleic acid molecule to be sequenced is followed in real time. The sequence is deduced by identifying which base is being incorporated into the growing complementary strand of the target nucleic acid by the catalytic activity of the nucleic acid polymerizing enzyme at each step in the sequence of base additions. A polymerase on the target nucleic acid molecule complex is provided in a position suitable to move along the target nucleic acid molecule and extend the oligonucleotide primer at an active site. A plurality of labelled types of nucleotide analogs are provided proximate to the active site, with each distinguishable type of nucleotide analog being complementary to a different nucleotide in the target nucleic acid sequence. The growing nucleic acid strand is extended by using the polymerase to add a nucleotide analog to the nucleic acid strand at the active site, where the nucleotide analog being added is complementary to the nucleotide of the target nucleic acid at the active site. The nucleotide analog added to the oligonucleotide primer as a result of the polymerizing step is identified. The steps of providing labelled nucleotide analogs, polymerizing the growing nucleic acid strand, and identifying the added nucleotide analog are repeated so that the nucleic acid strand is further extended and the sequence of the target nucleic acid is determined. (Emphasis added)

49. Korlach et al., column 4, penultimate paragraph, teach that the polymerase lacks exonuclease activity (applicant's "the polymerizing agent lacks the ability to remove previously incorporated nucleotide."). Such a showing meets a limitation of claims 100 and 102-104.

50. Korlach et al., column 11, teach:

> [T]he continued presence of labels on nucleotide analogs complementing bases in the target nucleic acid that have already been sequenced would very likely interfere with the detection of nucleotide analogs subsequently added to the primer. Accordingly, labels added to the sequencing primer are removed after they have been detected, as shown in FIG. 2C. This preferably takes place before additional nucleotide analogs are incorporated into the oligonucleotide primer.

51. Korlach et al., column 14, last paragraph, bridging to column 16, teach:

> In addition to fluorescent labels that remain in the nucleic acid during synthesis, **nucleotides that are labelled fluorescently or otherwise and carry the label attached to either the beta or gamma phosphate of the nucleotide can also be used in the sequencing procedure of the present invention**… During the synthesis of DNA, the bond cleavage in the nucleotide occurs between the alpha and the beta phosphate, causing the beta and gamma phosphates to be released from the active site after polymerization, and the formed pyrophosphate subsequently diffuses or is convected away from the nucleic acid… As a result, the fluorescence of the label that is attached to the beta or gamma phosphate of the nucleotide analog remains proximate to the polymerase for a longer time in case the nucleotide analog is polymerized… **After incorporation, the label will diffuse away with the cleaved pyrophosphate…** The interaction between the fluorophore and the base quenches the fluorescence, so that the molecule is not very fluorescent in solution by itself. However, when such a fluorescent nucleotide is incorporated into the nucleic acid, the fluorophore gets disconnected from the nucleotide and the fluorescence is no longer quenched. For the case of a linkage to the beta or gamma phosphate of the nucleotide, this occurs naturally through the enzymatic activity of the polymerase… (Emphasis added)

Such a showing fairly teaches the limitation that the label attached to the nucleotide (applicant's "first tag") "is released during incorporation" (limitation of claims 10, as well as dependent claims 17 and 18).

The above argument fairly rebuts applicant's argument at page 14 of the response that Korlach et al., do not teach cleavage of that portion of the nucleotide that comprises the label.

52. Korlach et al., column 12, teach:

> Suitable techniques for detecting the fluorescent label include time-resolved far-field microspectroscopy, near-field microspectroscopy, **measurement of fluorescence**

> **resonance energy transfer**, photoconversion, and measurement of fluorescence lifetimes. Fluorophore identification can be achieved by spectral wavelength discrimination, measurement and separation of fluorescence lifetimes, fluorophore identification, and/or background suppression. (Emphasis added; limitation of claims 10 and 17-18)

53. Korlach et al., column 26, teach:

> **Detection of fluorescence resonance energy transfer (FRET) from a donor fluorophore (e.g., a donor attached to the polymerase) to adjacent nucleotide analog acceptors** that are incorporated into the growing nucleic acid strand suggests a further elegant possibility of lowering background from incorporated nucleotides. (Emphasis added)

The aspect that FET occurs speaks directly to the proximity of the bound label/tag on the polymerase to the tag bound to the pyrophosphate.

54. For the above reasons, and in the absence of convincing evidence to the contrary, claims 10, 17 and 18 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 7,033,764 B2 (Korlach et al.).

55. Claims 16, 50, 51, 53-55, 64, 65, 69, 71, 72, 74, 75, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 7,033,764 B2 (Korlach et al.).

56. Korlach et al., abstract, teaches:

> The present invention is directed to a method of sequencing a target nucleic acid molecule having a plurality of bases. In its principle, the temporal order of base additions during the polymerization reaction is measured on a molecule of nucleic acid, i.e. the activity of a nucleic acid polymerizing enzyme on the template nucleic acid molecule to be sequenced is followed in real time. The sequence is deduced by identifying which base is being incorporated into the growing complementary strand of the target nucleic acid by the catalytic activity of the nucleic acid polymerizing enzyme at each step in the sequence of base additions. A polymerase on the target nucleic acid molecule complex is provided in a position suitable to move along the target nucleic acid molecule and extend

> the oligonucleotide primer at an active site. A plurality of labelled types of nucleotide analogs are provided proximate to the active site, with each distinguishable type of nucleotide analog being complementary to a different nucleotide in the target nucleic acid sequence. The growing nucleic acid strand is extended by using the polymerase to add a nucleotide analog to the nucleic acid strand at the active site, where the nucleotide analog being added is complementary to the nucleotide of the target nucleic acid at the active site. The nucleotide analog added to the oligonucleotide primer as a result of the polymerizing step is identified. The steps of providing labelled nucleotide analogs, polymerizing the growing nucleic acid strand, and identifying the added nucleotide analog are repeated so that the nucleic acid strand is further extended and the sequence of the target nucleic acid is determined. (Emphasis added)

57. Korlach et al., column 4, penultimate paragraph, teach that the polymerase lacks exonuclease activity (applicant's "the polymerizing agent lacks the ability to remove previously incorporated nucleotide."). Such a showing meets a limitation of claims 100 and 102-104.

58. Korlach et al., column 11, teach:

> [T]he continued presence of labels on nucleotide analogs complementing bases in the target nucleic acid that have already been sequenced would very likely interfere with the detection of nucleotide analogs subsequently added to the primer. Accordingly, labels added to the sequencing primer are removed after they have been detected, as shown in FIG. 2C. This preferably takes place before additional nucleotide analogs are incorporated into the oligonucleotide primer.

59. Korlach et al., column 14, last paragraph, bridging to column 16, teach:

> In addition to fluorescent labels that remain in the nucleic acid during synthesis, **nucleotides that are labelled fluorescently or otherwise and carry the label attached to either the beta or gamma phosphate of the nucleotide can also be used in the sequencing procedure of the present invention**… During the synthesis of DNA, the bond cleavage in the nucleotide occurs between the alpha and the beta phosphate, causing the beta and gamma phosphates to be released from the active site after polymerization, and the formed pyrophosphate subsequently diffuses or is convected away from the nucleic acid… As a result, the fluorescence of the label that is attached to the beta or gamma phosphate of the nucleotide analog remains proximate to the polymerase for a longer time in case the nucleotide analog is polymerized… **After incorporation, the label will diffuse away with the cleaved pyrophosphate…** The interaction between the fluorophore and the base quenches the fluorescence, so that the molecule is not very fluorescent in solution by itself. However, when such a fluorescent nucleotide is

> incorporated into the nucleic acid, the fluorophore gets disconnected from the nucleotide and the fluorescence is no longer quenched. For the case of a linkage to the beta or gamma phosphate of the nucleotide, this occurs naturally through the enzymatic activity of the polymerase… (Emphasis added)

Such a showing fairly teaches the limitation that the label attached to the nucleotide (applicant's "first tag") "is released during incorporation" (limitation of claims 10, as well as dependent claims 17 and 18).

The above argument fairly rebuts applicant's argument at page 14 of the response that Korlach et al., do not teach cleavage of that portion of the nucleotide that comprises the label.

60. Korlach et al., column 12, teach:

> Suitable techniques for detecting the fluorescent label include time-resolved far-field microspectroscopy, near-field microspectroscopy, **measurement of fluorescence resonance energy transfer**, photoconversion, and measurement of fluorescence lifetimes. Fluorophore identification can be achieved by spectral wavelength discrimination, measurement and separation of fluorescence lifetimes, fluorophore identification, and/or background suppression. (Emphasis added; limitation of claims 10 and 17-18)

61. Korlach et al., column 26, teach:

> **Detection of fluorescence resonance energy transfer (FRET) from a donor fluorophore (e.g., a donor attached to the polymerase) to adjacent nucleotide analog acceptors** that are incorporated into the growing nucleic acid strand suggests a further elegant possibility of lowering background from incorporated nucleotides. (Emphasis added)

The aspect that FET occurs speaks directly to the proximity of the bound label/tag on the polymerase to the tag bound to the pyrophosphate.

62. Korlach et al., have not been found to teach explicitly that the tag is covalently bound to the nucleotide (dNTP), yet it is required to be "released upon dNTP incorporation due to action of the polymerase." As set forth in paragraph 59, *supra*, the label (applicant's "tag") is bound to

the bets or gamma phosphate, and remains attached to said phosphate moieties upon cleavage of the pyrophosphate residues. Clearly, such language reasonably suggests that the label/tag is bound covalently to that part of the dNTP that is released upon dNTP incorporation due to action of the polymerase.

63. Attention is directed to the decision in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007):

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

64. It is further noted that prior art is not limited to the four corners of the documentary prior art being applied. Prior art includes both the specialized understanding of one of ordinary skill in the art, and the common understanding of the layman. It includes "background knowledge possessed by a person having ordinary skill in the art. . . [A] court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR* at 1396.

65. Suggestion, teaching or motivation does not have to be explicit and "may be found in any number of sources, including common knowledge, the prior art as a whole or the nature of the problem itself" *Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007) citing *Dystar Textilfarben GMBH v. C. H. Patrick Co.*, 464 F.3d 1356 (Fed. Cir. 2006).

66. In view of the explicit teachings of method of sequencing nucleic acids, using the same reagents and resulting in the same results- the determination of the nucleotide sequence of a

target nucleic acid in real time or near real time, and that the method does not result in any unexpected result, the claims invention is deemed to be obvious in view of the prior art of record.

Response to argument

67. At pages 15 and 16 of the response, argument is presented regarding the prior rejection of claims 108-111 under 35 USC 102(e)/103(c). These arguments are deemed moot by the withdrawal of the rejection of said claims.

68. At page 15 of the response applicant asserts that Korlach et al., does not make obvious the claimed invention, asserting in particular that Korlach et al., does not teach or suggest the cleavage of the label/tag from a nucleotide upon incorporation. While agreement is reaching hat Korlach et al., do explore the aspect of retaining the label on nucleotides during incorporation, they also teach explicitly of cleavage of the nucleotide by the polymerase at the time of incorporation. See paragraph 59, *supra*. In view of such explicit guidance one of ordinary skill in the art at the time of the invention, knowing of the difficulties to be encountered by retaining the label, would have been motivated to have used a system whereby the label is cleaved by the polymerase at the time of incorporation would thereby eliminating the issue associated with tags bound to incorporated nucleotides.

69. For the above reasons, and in the absence of convincing evidence to the contrary, claims 16, 50, 51, 53-55, 64, 65, 69, 71, 72, 74, 75, 77, 79-82, 84-87, 89-92, 95-98, 100, 102-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 7,033,764 B2 (Korlach et al.).

Conclusion

70. Objections and/or rejections which appeared in the prior Office action and which have not been repeated hereinabove have been withdrawn.

71. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

72. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

73. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571)272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

74. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

75. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/
Primary Examiner, Art Unit 1634